

# **STATISTICAL ANALYSIS PLAN**

**ANB019-002**

**A SINGLE ARM MULTIPLE DOSE STUDY TO ASSESS THE EFFICACY AND SAFETY OF ANB019 IN SUBJECTS WITH GENERALIZED PUSTULAR PSORIASIS**

**AUTHORS:**



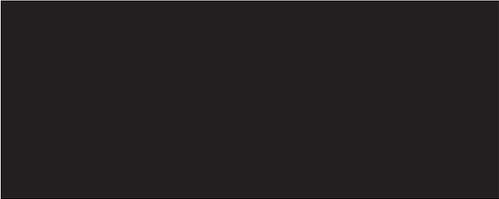
**VERSION NUMBER AND DATE: VERSION 0.4, 9SEP2019**

**National Clinical Trial (NCT) number: NCT03619902**

# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Version 1.0 (Dated 09Sep2019) for Protocol ANB019-002.

	Name	Signature	Date
<b>Author:</b>			
<b>Position:</b>			
<b>Company:</b>			

	Name	Signature	Date
<b>Author:</b>			
<b>Position:</b>			
<b>Company:</b>			

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
<b>Approved By:</b>			
<b>Position:</b>			
<b>Company:</b> Anaptys Bio, Inc.			

<b>Approved By:</b>			
<b>Position:</b>			
<b>Company:</b> Anaptys Bio, Inc.			

	Name	Signature	Date
<b>Approved By:</b>			
<b>Position:</b>			
<b>Company:</b> Anaptys Bio, Inc.			

## MODIFICATION HISTORY

<b>Unique Identifier for this Version</b>	<b>Date of Document Version</b>	<b>Authors</b>	<b>Significant Changes from Previous Authorized Version</b>
1.0	09Sep2019		Not Applicable – First Version

# TABLE OF CONTENTS

<b>1.</b>	<b>INTRODUCTION</b>	<b>7</b>
<b>2.</b>	<b>STUDY OBJECTIVES</b>	<b>7</b>
<b>2.1.</b>	<b>Primary Objectives</b>	<b>7</b>
<b>2.2.</b>	<b>Secondary Objectives</b>	<b>7</b>
<b>2.3.</b>	<b>Exploratory Objectives</b>	<b>7</b>
<b>3.</b>	<b>ENDPOINTS</b>	<b>8</b>
<b>3.1.</b>	<b>Primary Endpoints</b>	<b>8</b>
3.1.1.	Primary Efficacy Endpoints	8
3.1.2.	Primary Safety	8
<b>3.2.</b>	<b>Secondary Endpoints</b>	<b>8</b>
<b>3.3.</b>	<b>Exploratory Endpoints</b>	<b>8</b>
<b>4.</b>	<b>HYPOTHESIS</b>	<b>9</b>
<b>5.</b>	<b>STUDY DESIGN</b>	<b>9</b>
<b>5.1.</b>	<b>General Description</b>	<b>9</b>
<b>5.2.</b>	<b>Sample size</b>	<b>10</b>
<b>5.3.</b>	<b>Schedule of Activities</b>	<b>10</b>
<b>5.4.</b>	<b>Changes to Analysis from Protocol</b>	<b>10</b>
<b>6.</b>	<b>STATISTICAL GENERAL CONSIDERATIONS</b>	<b>10</b>
<b>7.</b>	<b>PLANNED ANALYSES</b>	<b>11</b>
<b>7.1.</b>	<b>Data Monitoring Committee</b>	<b>11</b>
<b>7.2.</b>	<b>Interim Analysis</b>	<b>11</b>
<b>7.3.</b>	<b>Final Analysis</b>	<b>1</b>
<b>8.</b>	<b>ANALYSIS SETS</b>	<b>1</b>
<b>8.1.</b>	<b>Reference Dates and Study Day</b>	<b>2</b>
<b>8.2.</b>	<b>Baseline</b>	<b>2</b>
<b>8.3.</b>	<b>Retests, Unscheduled Visits and Early Discontinuation</b>	<b>2</b>
<b>8.4.</b>	<b>Windowing Conventions</b>	<b>3</b>
<b>8.5.</b>	<b>Statistical Tests</b>	<b>4</b>
<b>8.6.</b>	<b>Common Calculations</b>	<b>4</b>
8.6.1.	Change From Baseline at Visit X	4
8.6.2.	Percent Change From Baseline at Visit X	4

<b>8.7. Software Version</b>	<b>5</b>
<b>9. STATISTICAL CONSIDERATIONS</b>	<b>5</b>
9.1. Adjustments for Covariates to be Included in Analyses	5
9.2. Multicenter Studies	5
9.3. Missing data	5
9.4. Examination of Subgroups	5
9.5. Multiplicity	5
<b>10. OUTPUT PRESENTATIONS</b>	<b>6</b>
<b>11. DISPOSITION AND WITHDRAWALS</b>	<b>6</b>
<b>12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS</b>	<b>6</b>
<b>13. MEDICAL HISTORY</b>	<b>7</b>
<b>14. MEDICATIONS</b>	<b>7</b>
<b>15. STUDY MEDICATION EXPOSURE</b>	<b>8</b>
<b>16. STUDY MEDICATION COMPLIANCE</b>	<b>8</b>
<b>17. EFFICACY OUTCOMES</b>	<b>9</b>
<b>17.1. Primary Efficacy</b>	<b>9</b>
17.1.1. Response Based on Clinical Global Impression Scale	9
17.1.2. Missing Data Methods for Primary Efficacy Variable	10
17.1.3. Analysis of Primary Efficacy Variable	11
17.1.4. Sensitivity Analysis of Primary Efficacy Variable(s)	11
<b>17.2. Secondary Efficacy</b>	<b>11</b>
17.2.1. Secondary Efficacy Variables & Derivations	11
17.2.1.1. Change in mJDA Severity Index Total Skin Lesions Score At All Study Visits	11
17.2.1.2. Change in Affected BSA of Erythema With Pustules, Erythema, and Edema at All Study Visits	13
17.2.1.3. Change in Total and Individual Scores in Systemic Manifestations and Laboratory Findings as Measured by mJDA Severity Index at All Study Visits	14
17.2.1.4. Proportion of Subjects Achieving A GPPPGA Score of 0 or 1 at Post-Baseline Study Visits	15
17.2.1.5. GPPPGA Change from Baseline Scores at All Study Visits	15
17.2.1.6. PASI Score Summary	16
17.2.1.7. Improvement in DLQI Total Score at All Study Visits	17
17.2.2. Missing Data Methods for Secondary Efficacy Variable	18
17.2.3. Analysis of Secondary Efficacy Variables	18
<b>17.3. Exploratory Efficacy</b>	<b>18</b>
17.3.1. Photographic documentation of lesions	18
<b>18. PHARMACOKINETICS</b>	<b>19</b>
<b>18.1. Variables &amp; Derivations</b>	<b>19</b>
18.1.1. Serum Concentration Data	19
18.1.2. Pharmacokinetic Parameters	19
<b>18.2. Missing Data Methods</b>	<b>21</b>
<b>18.3. Deviations Related to PK</b>	<b>22</b>
<b>18.4. Analysis of PK Parameters</b>	<b>22</b>

<b>18.5. Precision of PK Variables</b>	<b>22</b>
<b>19. SAFETY OUTCOMES</b>	<b>23</b>
19.1.1. Treatment Emergent Adverse Events	24
19.1.2. TEAEs Leading to Discontinuation of Treatment	25
19.1.3. TEAEs Leading to Withdrawal of Subjects	25
19.1.4. Infusion Related AEs/injection site reactions	25
19.1.5. Adverse Events of Special Interest	25
19.1.6. Serious Adverse Events	25
19.1.7. AEs Leading to Death	26
19.1.8. Disease Related AEs	26
<b>19.2. Laboratory Evaluations</b>	<b>26</b>
19.2.1. Laboratory Specific Derivations	26
19.2.2. Laboratory Reference Ranges	27
<b>19.3. ECG Evaluations</b>	<b>27</b>
<b>19.4. Vital Signs</b>	<b>27</b>
<b>19.5. Physical Examination</b>	<b>28</b>
<b>19.6. Other Safety Assessments</b>	<b>28</b>
19.6.1. Biomarker Analysis	28
19.6.2. Immunogenicity Analysis	28
<b>20. GENETIC ANALYSIS</b>	<b>29</b>
<b>20.1. GPP Associated Mutations</b>	<b>29</b>
<b>21. DATA NOT SUMMARIZED OR PRESENTED</b>	<b>29</b>
<b>22. REFERENCES</b>	<b>30</b>
<b>APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS</b>	<b>31</b>
<b>Output Conventions</b>	<b>31</b>
<b>Dates &amp; Times</b>	<b>37</b>
<b>Spelling Format</b>	<b>37</b>
<b>Presentation of Treatment Groups</b>	<b>37</b>
<b>Presentation of Visits</b>	<b>37</b>
<b>Listings</b>	<b>38</b>
<b>APPENDIX 2. PARTIAL DATE CONVENTIONS</b>	<b>39</b>
<b>Algorithm for Treatment Emergent Adverse Events</b>	<b>39</b>
<b>Algorithm for Prior/Concomitant Medications</b>	<b>40</b>

# 1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy, pharmacokinetics (PK), safety and immunogenicity data for Protocol ANB019-002, Amendment 4, dated 30 August 2019.

Changes to the protocol that impact the design, the data collected, or the statistical methods that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the protocol.

## 2. STUDY OBJECTIVES

### 2.1. PRIMARY OBJECTIVES

- To evaluate the efficacy of ANB019 in subjects with active Generalized Pustular Psoriasis (GPP) as measured by the Clinical Global Impression (CGI) scale according to the modified Japanese Dermatology Association (mJDA) severity index total score.
- To assess the safety and tolerability of ANB019 in subjects with GPP.

### 2.2. SECONDARY OBJECTIVES

- To evaluate the effect of ANB019 on the total and individual skin lesion symptoms as measured by the modified JDA severity index score.
- To evaluate the effect of ANB019 on total and individual components of systemic manifestations and laboratory findings as measured by mJDA severity index score.
- To evaluate the effect of ANB019 on GPP using the Generalized Pustular Psoriasis Physician's Global Assessment (GPPPGA).
- To determine any treatment effect of ANB019 in plaque psoriasis (if present) as measured by Psoriasis Area Severity Index (PASI).
- To assess the effect of ANB019 on the subject's quality of life (QOL).
- To describe the pharmacokinetics (PK) of ANB019 in GPP subjects.
- To test for immunogenicity to ANB019.

### 2.3. EXPLORATORY OBJECTIVES

- To explore the effects of ANB019 on skin biopsy biomarkers.
- To assess the effect of ANB019 on inflammatory parameters such as serum cytokines including, but not limited to, IL-8.
- Provide photographic documentation of lesions.
- To explore GPP-associated mutations and additional pharmacogenomic analysis.

## **3. ENDPOINTS**

### **3.1. PRIMARY ENDPOINTS**

#### **3.1.1. PRIMARY EFFICACY ENDPOINTS**

- Proportion of subjects achieving clinical response at Week 4 and Week 16, where clinical response is defined as “Very much improved”, “Much improved”, and “Minimally improved” on CGI scale according to modified JDA severity index total score.

#### **3.1.2. PRIMARY SAFETY**

- Assessment of adverse events (AEs).
- Potentially significant and clinically important AEs, including adverse events of special interest (AESI), serious adverse events (SAEs), and AEs leading to withdrawal.
- Physical examinations
- Vital signs
- 12-lead electrocardiogram (ECG)
- Clinical safety laboratory tests (hematology, biochemistry, and urinalysis)

### **3.2. SECONDARY ENDPOINTS**

- Change in modified JDA severity index total skin lesions score (sum of erythema, erythema with pustules, edema) at all study visits
- Change in affected body surface area (BSA) of erythema with pustules, erythema, and edema as measured by modified JDA severity index at all study visits
- Change in total and individual scores in systemic manifestations and laboratory findings as measured by modified JDA severity index at all study visits
- Proportion of subjects achieving a GPPPGA score of 0 or 1 at all study visits
- Change from baseline in GPPPGA scores at all study visits
- Change in PASI score to evaluate a subject’s overall plaque psoriasis disease state, if present, at all study visits
- Change in Dermatology Life Quality Index (DLQI) total score at all study visits
- Serum concentration following ANB019 administration.
- Maximum observed concentration (C<sub>max</sub>), time to maximum observed concentration (t<sub>max</sub>), area under the concentration-time curve (AUC) and other PK parameters as appropriate
- Presence of anti-drug antibodies (ADA) compared to baseline

### **3.3. EXPLORATORY ENDPOINTS**

- Skin biopsy biomarkers (including but not limited to IL-17, IL-23, IL-8, dendritic cells, epidermal thickness, and leukocytes infiltration)
- Changes in serum cytokines as compared to Baseline at Weeks 1, 4, 8, 12, 16, and 24
- Photographic documentation of lesions
- Optional genetic testing (DNA and mRNA)

## 4. HYPOTHESIS

No formal hypothesis testing will be performed.

## 5. STUDY DESIGN

### 5.1. GENERAL DESCRIPTION

This is an open-label, single arm, multiple dose study to assess the clinical efficacy, as well as the safety, tolerability, and PK of multiple doses of ANB019 in subjects with GPP.

The screening period will be up to 42 days (6 weeks) prior to administration of study drug on Day 1. Written informed consent will be obtained from each subject prior to initiating any study related procedures. All screening procedures will be conducted in accordance with the Schedule of Activities (see Section 1.3 in the protocol). On Day 1, subjects who meet the entry criteria will receive a 750 mg IV dose of ANB019 in an open-label manner, followed by 3 doses of 100 mg SC administered on Days 29, 57, and 85.

Subjects will leave the study center after completion of the 5 hours postdose assessments following IV administration and the 3 hours postdose assessments after the first and second SC injections and with the investigator's approval. Subjects with any ongoing AEs or SAEs at the time of scheduled discharge from the study center should remain at the study center until the Investigator has determined that these events have resolved or are deemed as not clinically significant.

After completing Day 1 assessments, the subjects will return to the study center for follow-up visits on Days 3, 8, weekly from Day 8 to Day 29, every other week up to Day 85, then monthly for 12 weeks to monitor changes in disease activity, safety, and tolerability. In addition, subjects will be contacted via phone by study staff to assess for safety (e.g., AEs and changes in concomitant medications) on Days 36, 50, 64, and 78.

Subjects who are non-responders at Week 4 will be early terminated 4 weeks after the 750 mg IV dose administration. A non-responder is defined as a subject who experiences:

- “No change” on Clinical Global Impression (CGI): 0 points change in JDA total score and not meeting “other criteria” for minimally improved.
- “Worsened” based on CGI:  $\geq 1$ -point increase in JDA total score.

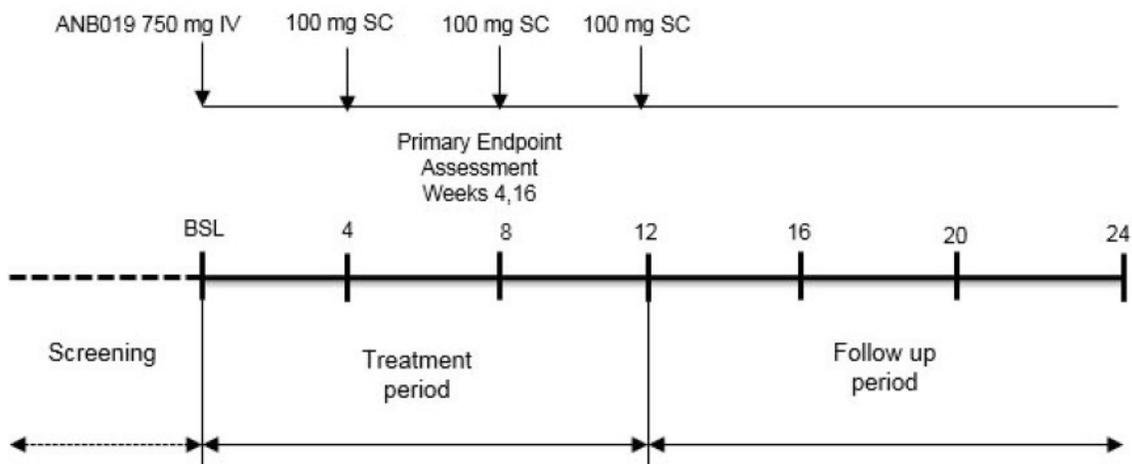
Disease activity (response to study treatment) will be evaluated using the CGI scale according to the mJDA severity index, change in total area of erythema with pustules, erythema, and edema as measured by modified JDA index, systemic manifestations and laboratory findings as per modified JDA severity index, GPPPGA scale, and PASI score (if PP is present). Quality of life (QoL) will be assessed using the DLQI.

Serum samples for PK and immunogenicity will be collected before the administration of ANB019 and at the other time points specified in the Schedule of Activities (see Section 1.3 in the protocol). Refer to Table 2 in the protocol for additional information on sample collection and time points. All subjects enrolled in the study will be asked to participate in the skin biopsy and/or genetic analysis; however, participation is optional, and subjects will be asked to give specific consent for these assessments.

Safety assessments including AE/SAE monitoring, vital signs measurements, physical examination, ECGs, laboratory measurements, and urine assessments will be performed during the study.

The EOS visit will be on Day 169 and all subjects will return to the study center for the EOS procedures (see Section 1.3 in the protocol and Figure 1 below for more details).

Figure 1. Study Schema



Abbreviations: BSL = baseline; IV = intravenous, SC = subcutaneous.

## 5.2. SAMPLE SIZE

The sample size is not based on statistical power considerations. Approximately 10 subjects will be enrolled at 8 study centers for study treatment.

## 5.3. SCHEDULE OF ACTIVITIES

Please refer to Section 1.3 in the protocol

## 5.4. CHANGES TO ANALYSIS FROM PROTOCOL

There are no changes from the analysis mentioned in the protocol.

## 6. STATISTICAL GENERAL CONSIDERATIONS

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor with this SAP.

Coding of AEs and medical history will be done by Medical Dictionary for Regulatory Activities (MedDRA) directory Version 22 (or higher) and medications data by the World Health Organization (WHO)-drug dictionary dated Mar2019 (or higher) by ████████<sup>TM</sup>.

The default summary statistics for continuous variables include number of contributing observations (n), mean,

standard deviation (SD), median, minimum, and maximum or as described in the respective section. For categorical variables, the number and percentage (the percentage of subjects in each category relative to the total number of subjects in the relevant analysis set, or relative to the total number of subjects in the relevant analysis set and with assessments available [where appropriate]) in each category will be the default summary presentation.

In general, for non-PK data, the number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of decimal places allotted in the raw data received from data management.
- SD: 2 more than the number of decimal places allotted in the raw data.
- Minimum and maximum: equal to the number of decimal places allotted in the raw data.
- Percentages: All percentages between 0 and 100 will be rounded to 1 decimal unless there is a need to report more than 1 decimal for percentages.
- Reference ranges will be reported to the same number of decimal places displayed by the laboratory.
- *P* values and confidence intervals (CIs), if any, will be reported to 4 decimal places. *P* values less than 0.0001 will be presented as “<0.0001” and *p* value greater than 0.9999 will be presented as “1.0000”.

Data from subjects excluded from an analysis set will be included in the data listings, but not in the summaries. Concentration versus time summaries will be presented for all subjects in the PK Analysis Set (PKAS). Reporting standards for PK data (ANB019 concentrations) is described in Section 18.

## **7. PLANNED ANALYSES**

### **7.1. DATA MONITORING COMMITTEE**

No Data Monitoring Committee is planned for this study.

### **7.2. INTERIM ANALYSIS**

An interim analysis will be performed when approximately 50% of subjects have completed their Week 4 visit or when at least 2 subjects have reached 16 weeks postdosing. The interim analysis will assess primary efficacy and all safety data. Data from interim analyses might be used as a guideline for possible protocol modifications and planning of future clinical studies.

### 7.3. FINAL ANALYSIS

Final analysis will be performed once all subjects complete the efficacy, safety, PK and immunogenicity evaluations described in the protocol.

Planned analyses identified in this SAP will be performed by [REDACTED] Biostatistics following AnaptysBio authorization of this SAP.

## 8. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set (Table A below) will be conducted in preparation for the IA to be performed when at least 50% of subjects complete their safety and efficacy Week 4 assessments, or at least 2 subjects have completed their Week 16 assessments, and again after all subjects have completed the study for the final analysis.

Table A. Analysis Sets

Full Analysis Set (FAS)	The FAS analysis set will include all subjects, regardless of whether or not the treatment was received. Subjects will be analyzed based on treatment received.
Safety Analysis Set (SAF)	The Safety analysis set will include all enrolled subjects who received at least 1 dose of ANB019. The Safety Analysis Set will be used for all safety analyses. Subjects will be analyzed as treated.
Per Protocol Analysis Set (PPS)	The Per Protocol analysis set will include all subjects in the FAS analysis set who do not have major protocol violations that would affect the evaluation of the primary efficacy endpoint.
PK Analysis Set (PKAS)	The PK analysis set will include all subjects in the Safety analysis set who have at least 1 quantifiable PK sample available and who do not have events or deviations with the potential to affect PK concentrations. The PK analysis set will be used for all PK analyses.

### **8.1. REFERENCE DATES AND STUDY DAY**

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. The Reference start date (Day 1) is defined as the day of the first dose of study medication and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date, then:

$$\text{Study Day} = (\text{date of event} - \text{reference date}) + 1$$

If the date of the event is prior to the reference date, then:

$$\text{Study Day} = (\text{date of event} - \text{reference date})$$

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings.

### **8.2. BASELINE**

Unless otherwise specified, Baseline is defined as the last non-missing measurement taken prior to the Reference Start Date and time (including unscheduled assessments).

Where the last non-missing measurement and the Reference Start Date coincide, that measurement will be considered pre-Baseline unless there is conclusive evidence that the measurement was post study treatment administration.

Adverse events (AEs) and medications commencing on the Reference Start Date will be considered post-Baseline.

On Day 1 all assessments, except for the post-dose PK samples, should be taken before study treatment administration.

### **8.3. RETESTS, UNSCHEDULED VISITS AND EARLY DISCONTINUATION**

In general, for by-visit summaries and figures, data recorded at the nominal visit will be presented. In the

event of a retest of the same sample due to e.g. a laboratory error (same visit number assigned), the last usable assessment will be used. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the Baseline, EOS, End of Treatment (EOT) and Last Observation Carried Forward (LOCF) values, or best/worst case value where required (e.g. shift tables).

Listings will include scheduled, unscheduled and early discontinuation data, with unscheduled visits sorted chronologically.

#### 8.4. WINDOWING CONVENTIONS

Visit windows are assigned based on the Protocol SOA, and are presented in

Table B. Visit Windows

Table B. Visit Windows

Assigned Visit	Assigned Week	Study SOA day(s)	Study day(s)
D1/W0 (Screening)	-42 to 0	-28 to 0	-42 to 0
D1-W0 (Treatment)	0	0	1
D3-W1 (Treatment)	1	0	3
D8-W1 (Treatment)	1	0	8
D15-W2 (Treatment)	2	±1	15
D22-W3 (Treatment)	3	±1	22
D29-W4 (Treatment)	4	±2	29
D36-W5 (Treatment)	5	±2	36
D43-W6 (Treatment)	6	±2	43
D50-W7 (Treatment)	7	±2	50

Assigned Visit	Assigned Week	Study SOA day(s)	Study day(s)
D57-W8 (Treatment)	8	±2	57
D64-W9 (Treatment)	9	±2	64
D71-W10 (Treatment)	10	±2	71
D78-W11 (Treatment)	11	±2	78
D85-W12 (Treatment)	12	±2	85
D113-W16 (Follow up)	16	±2	113
D141-W20 (Follow up)	20	±2	141
D169-W24/EOS/ET (Follow up)	24	±2	169

## 8.5. STATISTICAL TESTS

This is an exploratory study and no formal hypothesis testing will be performed. Mean (SD) and nominal p-value will be reported where applicable. The data will be presented in summarized tabulated manner for trends and response patterns.

## 8.6. COMMON CALCULATIONS

### 8.6.1. CHANGE FROM BASELINE AT VISIT X

For numerical variables, change from Baseline at Visit X will be calculated as follows:

**Change from Baseline = Test value at Visit X – Baseline value**

### **8.6.2. PERCENT CHANGE FROM BASELINE AT VISIT X**

Percent change from Baseline at Visit X will be calculated as follows:

**Percent change from Baseline = (Test value at Visit X – Baseline value) / Baseline value x 100**

### **8.7. SOFTWARE VERSION**

Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 6.4 or higher (Certara, Princeton, New Jersey). All other derivations, statistical analyses, summaries, listings and graphics will be generated using SAS® version 9.4 (SAS® Institute, Inc., Cary, North Carolina).

## **9. STATISTICAL CONSIDERATIONS**

### **9.1. ADJUSTMENTS FOR COVARIATES TO BE INCLUDED IN ANALYSES**

Due to the small size of the study, no adjustment for covariates will be made.

### **9.2. MULTICENTER STUDIES**

This study will be conducted by multiple investigators at multiple centers internationally. Data from all sites will be pooled for analysis.

### **9.3. MISSING DATA**

Missing safety data will not be imputed. Partial dates for safety data will be imputed as outlined in Appendix 2 of this analysis plan. Missing efficacy data will be handled as described in Section 17.1.2 of this analysis plan. Missing PK data will be handled as described in Section 18.2 of this analysis plan.

### **9.4. EXAMINATION OF SUBGROUPS**

No subgroup analyses will be performed for this study.

## 9.5. MULTIPLICITY

No formal hypothesis testing will be performed; therefore, no multiplicity adjustment is required.

## 10. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by [REDACTED] Biostatistics. Appendix 1 describes the conventions for presentation of data in outputs. Minor modifications may be made to the tables, figures, and listings to accommodate the data.

## 11. DISPOSITION AND WITHDRAWALS

All subjects who provided informed consent (ENR) will be accounted for in this study. Subject disposition will be listed and summarized, including:

- Total subjects screened
- Number of screen failures (subjects who consent to participate in the clinical study but are not subsequently entered in the study)
- Total of subjects in the FAS
- Total subjects ongoing (subjects ongoing at the time of the IA)
- Total number of subjects in the SAF
- Total number of subjects in the PPS
- Total number of subjects in the PK Analysis Set
- Total subjects who discontinue from study treatment
- Total subjects who discontinue from the study
- Protocol deviations (PD) as obtained from the CTMS PD log

PDs will be identified and discussed with the Investigator/AnaptysBio in PD review meetings to categorize them, and to finalize analysis set assignment.

A subject is considered to have completed the study if they have completed all scheduled study visits



including the last visit on Day 169.

## 12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other Baseline characteristics will be presented for the SAF. No statistical testing will be carried out for demographic or other Baseline characteristics.

The following demographic characteristics will be summarized and listed for this study:

- date of birth and age at informed consent
- gender
- height, weight and BMI;  $BMI (kg/m^2) = weight (kg) / [height (m)]^2$
- ethnicity and race

If the date of birth is partial, age will be calculated using the available parts of the date.

Baseline characteristics will include Baseline values of efficacy and safety variables. Continuous variables will be summarized using count, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

## 13. MEDICAL HISTORY

Medical history will be captured on the MH eCRF at Screening and coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medical History will be provided in a listing.

The duration of a smoker's smoking period will be calculated as follows:

**Smoking period duration in years = date of informed consent - smoking start date**

If the smoking start date is partial, only the available parts will be compared to the same parts of the date of informed consent.

Medical history for the SAF will be summarized and listed by System Organ Class (SOC), Preferred Term (PT), High Level Term and Lowest Level Term.

## 14. MEDICATIONS

Medications will be captured on the Prior and Concomitant Medications (CM) eCRF and coded using the latest version of the World Health Organisation (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system.

Prior and Concomitant medications will be identified as follows:

- ‘Prior’ medications are medications that stopped prior to the first dose of the study treatment.
- ‘Concomitant’ medications are medications which started prior to, on or after the first dose of study treatment, and continue after Day 1.

In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified as the worst case i.e. concomitant. See APPENDIX 2 for handling of partial dates for medications. All prior, concomitant and rescue medications for the SAF will be listed and summarized by ATC Level 2 categories and preferred name.

## 15. STUDY MEDICATION EXPOSURE

The duration of exposure in days will be calculated as follows:

**Duration of exposure in days =  
date of last study treatment administration – date of first study treatment administration + 1.**

The dates of first and last study treatment administration will be taken from the IP eCRF. Interruptions, compliance, and dose changes are not considered for duration of exposure. Exposure to study medication in days will be summarized for the SAF.

## 16. STUDY MEDICATION COMPLIANCE

Compliance with the study treatment will be presented for the SAF and calculated based on the total volume administered as captured on the IP eCRF. The 750mg IV loading dose of ANB019-002 is administered on Day 1 following dilution by the site pharmacist to a total volume of 100 ml with 0.9% sodium chloride.



Subject compliance to the loading dose will be calculated based on the total volume administered (e.g. 95 or 110 ml) as a percentage of the prescribed volume for that dose (100 ml). This will only be based on the volume injected, as the volume of ANB019 that has been diluted, is not captured.

The 3 follow-up doses of ANB019-002 are administered SC, 100 mg each in a 1 ml solution that is prepared by the IP manufacturer and provided in glass vials. Subject compliance to the follow-up doses will be calculated based on the total volume administered (e.g. 0.9 ml) as a percentage of the prescribed volume for that dose (1 ml). As the solution is prepared by the manufacturer, it is assumed that treatment administration will not exceed 1 ml. Overall compliance for a subject will not be calculated.

Compliance with the IV loading dose will be calculated as follows:

**Compliance with IV loading dose = Total ml administered / 100 ml x 100**

Compliance with each of the three SC follow-up doses will be calculated as follows:

**Compliance with SC follow-up dose = Total ml administered / 1 ml x 100**

## 17. EFFICACY OUTCOMES

### 17.1. PRIMARY EFFICACY

#### 17.1.1. RESPONSE BASED ON CLINICAL GLOBAL IMPRESSION SCALE

The primary efficacy endpoint is the proportion of subjects achieving clinical response at Weeks 4 and 16. The clinical response is defined as a composite score which considers both the CGI and reduction in the mJDA score (compared to Baseline) at that visit, and is classified as “Very much improved”, “Much improved”, or “Minimally improved” on the 5-point CGI scale (see **Table C. Clinical Global Impression**).

Table C. Clinical Global Impression

<b>Change in mJDA Severity Index Total score</b>	<b>and/or</b>	<b>CGI Category description</b>	<b>CGI scale and Responder status</b>
Reduction by 3 or >3 points	or	Clear or almost clear of signs of GPP	Very much improved  <b>Responder</b>
Reduction by 1 or 2 points	or	At least one of the following: Area of erythema with pustules (%) reduced by $\leq 30\%$ , or Clinically meaningful improvement in at least two other components of the mJDA severity index for GPP (area of erythema, area of edema, fever, white blood cells (WBC), C-reactive protein (CRP) and serum albumin (Alb)).	Much improved  <b>Responder</b>
0 points (no change)	and	At least one of the following: Area of erythema with pustules (%) reduced by $\leq 20\%$ , or Clinically meaningful improvement in at least one other component of the mJDA severity index for GPP (area of erythema, area of edema, fever, WBC, CRP, Alb)	Minimally improved  <b>Responder</b>
0 points (no change)	and	Not meeting the CGI criteria of “minimally improved”	No change  <b>Non-responder</b>
Increased $\geq + 1$ point		Not applicable	Worsened  <b>Non-responder</b>



### **17.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE**

If the Responder Status is missing for a subject due to Lost to Follow-Up or early discontinuation or any other reason, it will remain missing.

Subjects who are non-responders (i.e. rated as “No change” or “Worsened” on CGI) at Week 4 will be early terminated from the study. Their Responder Status at Week 16 will remain non-responder.

If the Baseline mJDA severity index total score is missing, Responder Status will be defined based on CGI alone.

### **17.1.3. ANALYSIS OF PRIMARY EFFICACY VARIABLE**

This is an exploratory study and no formal hypothesis testing will be performed. The primary efficacy analysis will be performed on the FAS (see Section 8). Descriptive summary statistics will be presented for the CGI. The number and proportion of subjects achieving clinical response will be summarized in tabular form for Weeks 4 and 16. Each subject’s CGI category will be plotted over all study visits.

The proportion of subjects having a clinical response at Weeks 4 and 16 will be derived using all subjects randomized and enrolled as the denominator for this calculation.

### **17.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)**

There will be no sensitivity analysis for this exploratory study.

## **17.2. SECONDARY EFFICACY**

### **17.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS**

#### **17.2.1.1. Change in mJDA Severity Index Total Skin Lesions Score At All Study Visits**

The mJDA severity index is used to determine the primary endpoint, but itself is not a primary efficacy



variable. Individual components of the mJDA severity index are used for secondary efficacy analysis. Table D shows the mJDA questionnaire.

Table D. Modified Japanese Dermatological Association (mJDA) Worksheet

	<b>Score</b>			
	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>
<b>Assessment of skin lesions</b>				
<b>Area of erythema with pustules</b>	0%	>0%, <10%	≥10%, <50%	≥50%
<b>Total area of erythema</b>	0%	>0%, <25%	≥25%, <75%	≥75%
<b>Area of edema</b>	0%	>0%, <10%	≥10%, <50%	≥50%
<b>Assessment of systemic manifestations and laboratory findings</b>				
<b>Fever (°C)</b>	<37.0	≥37.0, <38.5	≥38.5	n/a
<b>WBC count (/μL)</b>	<10 000	≥10 000, <15 000	≥15 000	n/a
<b>CRP (mg/dL)</b>	<0.3	≥0.3, <7.0	≥7.0	n/a
<b>Serum albumin (g/dL)</b>	≥3.8	<3.8, ≥3.0	<3.0	n/a

The scores (0 to 3 for skin lesions, and 0 to 2 for systemic manifestations and laboratory findings) as well as the actual values of all seven mJDA assessments will be captured in the eCRF.

The total score will be calculated as follows and is the sum of these 7 scores:

**Severity Index Total Score = Sum of scores for: Area of erythema with pustules, Total area of erythema, Area of edema, Fever, WBC count, CRP, Serum albumin**

**The severity index total score will be categorized as follows in the listings: 1-6 =Mild, 7-10 = Moderate, and 11-17 = Severe.**

**Severity Index Total score at Visit X = Sum of all 7 mJDA scores at Visit X.**

**Severity Index Total score at Baseline = Sum of all 7 mJDA Baseline scores.**

**Change at Visit X = Severity Index Total score at Visit X – Severity Index Total score at Baseline**

Descriptive statistics (including n, mean, SD, median, minimum, and maximum) will be presented for each measurement time for all study visits. Each subject's change in mJDA Severity Index Total score will be plotted over all study visits.

The change from Baseline in the mJDA severity index total skin lesions score is the sum of erythema, erythema with pustules, and edema scores. The change in score for each visit can range from -9 to 9 and will be calculated as follows:

**Total Skin Lesions Score at Visit X = Sum of the scores at Visit X for: Area of erythema with pustules, Total area of erythema, Area of edema.**

**Total Skin Lesions Score at Baseline = Sum of the scores at Baseline for: Area of erythema with pustules, Total area of erythema, Area of edema.**

**Change at Visit X = Total Skin Lesions Score at Visit X – Total Skin Lesions Score at Baseline**

Descriptive statistics (including n, mean, SD, median, minimum, and maximum) will be presented for each measurement time for all study visits. Each subject's change in mJDA total skin lesion score will be plotted over all study visits.

#### **17.2.1.2. Change in Affected Area of Erythema With Pustules, Erythema, and Edema at All Study Visits**

The change from Baseline in each of the measurements: percent area of erythema, percent area of erythema



with pustules, and percent area of edema at all study visits will be calculated.

The change for each visit for each area percentage will be calculated as follows:

Area % at Visit X = The percentage from the mJDA assessment.

Area % at Baseline = Total percentage from the mJDA assessment at Baseline

Change at Visit X = Area % at Visit X – Total area % at Baseline

Descriptive statistics (including n, mean, SD, median, minimum, and maximum) will be presented at each measurement time for all study visits. An overlay plot of each subject's value over all study visits will be presented for each component score.

### **17.2.1.3. Change in Total and Individual Scores in Systemic Manifestations and Laboratory Findings as Measured by mJDA Severity Index at All Study Visits**

The change from Baseline of the total and the four individual scores in systemic manifestations and laboratory findings, as measured by the mJDA at all study visits, will be summarized in the same manner as the change in mJDA severity index total skin lesions score.

Change in the total score for each visit can range from -8 to 8 and will be calculated with the following derivations:

**Total score at Visit X = Sum of scores at Visit X for: Fever, WBC count, CRP, Serum albumin**

**Total score at Baseline = Sum of scores at Baseline for: Fever, WBC count, CRP, Serum albumin**

**Change at Visit X = Total score at Visit X – Total score at Baseline**

Change in the four individual scores for each visit can range from -2 to 2 and will be calculated as follows:

**Fever Score Change at Visit X = Fever Score at Visit X – Fever Score at Baseline**

The same formula will be applied to calculate the **Score Change at Visit X** for the **WBC Count, CRP** and **Serum albumin**.

Descriptive statistics (including n, mean, SD, median, minimum, and maximum) will be presented at each measurement time at all study visits for each numeric systemic manifestation and laboratory finding. An overlay plot of each subject's value over study visits will be presented for each measurement at all study visits.

**17.2.1.4. Proportion of Subjects Achieving A GPPPGA Score of 0 or 1 at Post-Baseline Study Visits**

The GPPPGA is a physician-based assessment of GPP, performed at every visit (except phone calls). The severity and impact of the subject’s erythema, pustules, and scaling/crusting of pustular psoriasis lesions is scored on a 5-point scale as shown below in **Table E. Scoring of GPPPGA**.

Table E. Scoring of GPPPGA

Score	Wording	Detailed description
0	Clear	Normal skin or post-inflammatory hyperpigmentation, no visible pustules, no scaling or crusting
1	Almost clear	Faint, diffuse pink or slight red erythema, low density occasional small discrete pustules (non-coalescent), superficial focal scaling or crusting restricted to periphery of lesions
2	Mild	Light red erythema, moderate density grouped discrete small pustules (non-coalescent), predominantly fine scaling or crusting
3	Moderate	Bright red erythema, high density pustules with some coalescence, moderate scaling or crusting covering most or all lesions
4	Severe	Deep fiery red erythema, very high-density pustules with pustular lakes, severe scaling or crusting covering most or all lesions

The GPPPGA will be summarized at each post-baseline visit for the proportion of subjects achieving a score of 0 or 1 as opposed to a 2, 3 or 4. The proportion of subjects having a GPPPGA score of 0 or 1 will be derived using all subjects randomized and enrolled as the denominator for this calculation.

**17.2.1.5. GPPPGA Change from Baseline Scores at All Study Visits**

The change from Baseline in GPPPGA will be summarized at each postbaseline visit. A separate overlay



plot will display each subject’s GPPPGA score over all study visits and another for each subject’s change from baseline scores over all study visits.

**17.2.1.6. PASI Score Summary**

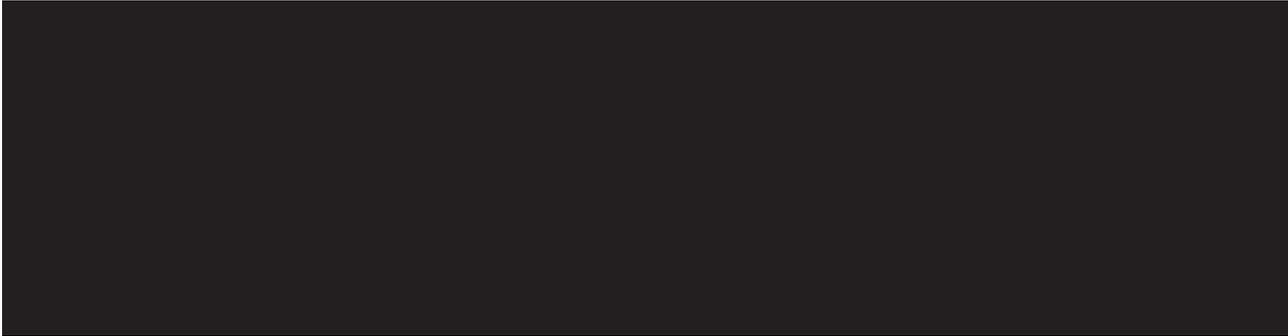
PASI scores will be used to determine the treatment response in subjects with plaque psoriasis. The PASI total score includes 12 plaque characteristic (i.e. erythema, induration, scaling) scores and four percentages of BSA affected.

**Table F Psoriasis Area Severity Index Score (PASI)** shows the PASI worksheet. Details for these calculations appear in the PASI worksheet. If any of the values to be calculated are missing (A, C and D in the PASI worksheet, as well as the total PASI score), they will be calculated by [REDACTED] Biostatistics.

Summary statistics will be provided for absolute PASI scores as well as for percent change from Baseline for all study visits.

Table F Psoriasis Area Severity Index Score (PASI)

Plaque characteristic	Lesion score	Head	Upper limbs	Trunk	Lower limbs
Erythema	<b>0 = None</b> <b>1 = Slight</b> <b>2 = Moderate</b> <b>3 = Severe</b> <b>4 = Very severe</b>				
Induration/Thickness					
Scaling					
<i>Add together the 3 scores for each body region to give the <b>Lesion Score Sums (A)</b> below:</i>					
<b>Lesion Score Sum (A)</b>					
Percent area affected	Area score (B)	Head	Upper limbs	Trunk	Lower limbs



<b>Degree of involvement as a % for each body region affected. Score each region with value between 0-6.</b>	<b>0 = 0%</b> <b>1 = 1% - 9%</b> <b>2 = 10% - 29%</b> <b>3 = 30% - 49%</b> <b>4 = 50% - 69%</b> <b>5 = 70% - 89%</b> <b>6 = 90% - 100%</b>				
<i>Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual Subtotals (C).</i>					
<b>Subtotals (C)</b>					
<b>Body Surface Area Value</b>	0.1	0.2	0.3	0.4	
Multiply each body region's <b>Subtotal (C)</b> by its <b>Body Surface Area Value</b> , i.e. x 0.1 for head, x 0.2 for upper limbs, x 0.3 for trunk, and x 0.4 for lower limbs.					
<b>Totals (D)</b>					
Add together the four body region scores in <b>Totals (D)</b> to give the final PASI Score.					

The total PASI Score will be calculated as follows:

**PASI Score = D for Head + D for Upper limbs + D for Trunk + D for Lower limbs**

**17.2.1.7. Change in DLQI Total Score at All Study Visits**

Dermatology QOL is assessed using the Dermatology Life Quality Index (DLQI, see protocol Appendix 12). Subjects will complete the DQLI questionnaire, consisting of 10 questions, at all visits.

Each question will be scored as follows:

<b>Item</b>	<b>Score</b>
Very much	3



Item	Score
A lot	2
A little	1
Not at all / Not relevant	0

- Additional scoring notes:
- A “No” at the first part of question 7 will be scored as a 0 or if “Yes” scored a 3.
- If the second part of question 7 was not answered due to answering “Not relevant” or “Yes” at the first part, it will be scored as a 0.
- The DLQI total score can range from 0 to 30 and will be derived as follows:

**DLQI total score = Sum of scores for Q1 to Q10**

The higher the total score, the more impaired dermatology QOL is. The change in score between visits will indicate the effect of ANB019 on the subject’s dermatology QoL. Summary statistics will be provided for total and average DLQI scores as well as for percent change from Baseline for all study visits.

**17.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE**

If GPPPGA score is missing for a subject, for any reason, the score will not be imputed. Missing values for DLQI will be replaced using Last Observation Carried Forward (LOCF) for summarization of the results. All other missing values for secondary efficacy assessments will remain missing and not be imputed for any summary calculations.

**17.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES**

All secondary efficacy analysis will be performed on the FAS (see Section 8).



## 17.3. EXPLORATORY EFFICACY

### 17.3.1. PHOTOGRAPHIC DOCUMENTATION OF LESIONS

Photography of the lesions will be performed for documentation purposes only. This will not be shared with [REDACTED] Biostatistics for analysis.

## 18. PHARMACOKINETICS

Derivation of serum PK parameters following ANB019 treatment will be the responsibility of the clinical pharmacokineticist at [REDACTED]. The PK summaries, summary figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of the study biostatistician at [REDACTED]. Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

### 18.1. VARIABLES & DERIVATIONS

#### 18.1.1. SERUM CONCENTRATION DATA

A subject listing of all concentration-time data following IV and SC injections will be presented by subject and scheduled sample collection time. Concentration data of ANB019 will be summarized by route/day and nominal time point using N (sample size), n (available data), arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum, median, maximum, and geometric mean using the respective PKAS. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Graphs for ANB019 mean concentration-time data following IV administration will be presented in linear and semi-logarithmic scale. Trough concentrations following and including Day 29 will be presented as scatter plots. By-subject plots will be presented in linear and semi-logarithmic scale.



### 18.1.2. PHARMACOKINETIC PARAMETERS

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

For PK parameter calculations following IV dose:

- Concentrations that are BLQ or missing at pre-dose or the beginning of the curve will be set to zero.
- Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile.
- A BLQ value that occurs between quantifiable data points, especially prior to  $C_{max}$ , will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted.
- Following  $C_{max}$ , BLQ values embedded between two quantifiable data points will be treated as missing when calculating PK parameters.
- If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero.
- If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

The following PK parameters will be calculated following IV administration of ANB019 by non-compartmental methods, using actual elapsed time from dosing.

$C_{max}$	Maximum observed concentration, obtained directly from the observed concentration versus time data.
$t_{max}$	Time of maximum observed concentration, obtained directly from the observed concentration versus time data.
$t_{1/2}$	Apparent terminal half-life (h), determined as $(\ln 2 / \lambda z)$
CL	Systemic clearance (L/h) calculated as $dose / AUC_{(0-last)}$
$V_z$	Volume of distribution (L) during terminal phase, estimated by dividing the systemic clearance by $\lambda z$ .
$\lambda z$	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve.
$AUC_{(0-last)}$	Area under the concentration-time curve (AUC) from time zero (pre-dose) to time of last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
AUCoverall	Area under the concentration-time curve (AUC) from time zero (pre-dose) on Day 1 (IV dose) to time of last quantifiable concentration following Day 87 SC dose
Note: The data from Day 1 to Day 29 pre-dose will be used to calculate the first 7 parameters.	

Details of any future population PK modeling and potential pharmacodynamic (PD) and/or efficacy/safety correlative exploratory analyses will be described in a separate modeling and simulation analysis plan that will be considered separate from this study SAP. Results from any population PK analysis and correlation with PD/efficacy/safety results will be presented in a PK modeling and simulation report that will be separate from the main clinical study report.

## 18.2. MISSING DATA METHODS

Missing pharmacokinetic data will not be imputed. Further discussion of treatment of missing data is dealt in Section 18.1.2



### 18.3. DEVIATIONS RELATED TO PK

Changes to the procedures or events which may impact the quality of the PK data, that will be considered significant with respect to PK will be described within the clinical study report body text.

These changes or events include any circumstances that could alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate or missed dosing on or before the day of PK sampling. In the case of a significant PD or event, PK data collected during the affected time period will be excluded from the study summaries.

Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant with respect to PK.

### 18.4. ANALYSIS OF PK PARAMETERS

A subject listing of individual PK parameters for each treatment will be provided. PK parameters for IV administration will be summarized for the respective PKAS using descriptive statistics, including N, n, mean, SD, CV%, median, minimum, maximum, geometric mean and geometric CV%, with the exception of  $t_{max}$ , which will be reported with N, n, minimum, median and maximum, only.

Parameters may be summarized based on anti-drug antibodies (ADA) status (i.e. overall and for positive/negative status). Pharmacokinetic parameters will not be summarized if  $n < 3$ .

Scatter plots of individual and geometric mean PK parameters ( $C_{max}$ ,  $AUC_{(0-last)}$ ) following IV administration will be presented. Additionally, graphical presentations of PK data may be added at the discretion of the PK scientist, if further illustration of the PK results is deemed appropriate.

### 18.5. PRECISION OF PK VARIABLES

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-subject listings. The unrounded derived PK data will be considered the source data for the calculation of descriptive statistics.

For most derived PK parameters, 33 significant digits will be used as the standard rounding procedure for listings, with the following exceptions:

- Parameters directly derived from source data (e.g.,  $C_{\max}$ ) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g.,  $t_{\max}$ ) will be reported to 2 decimal places with units of hours.

For the reporting of descriptive statistics for concentration and PK parameter variables:

- The mean, SD, and geometric mean will be presented to one digit more precision than the source data.
- The minimum, median, and maximum will be presented to the same precision as the source data.
- CV and geometric CV% will always be reported to one decimal place.

## 19. SAFETY OUTCOMES

All safety data (AEs, SAEs, vital signs, ECGs, and clinical laboratory assessments at each specific time point) will be listed and summarized descriptively using the SAF. All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Authorities (MedDRA). For the handling of partial dates for AEs, see Appendix 2 of this document.

All AEs will be classified by Intensity, Seriousness and Causality.

Intensity will be assessed as Mild, Moderate or Severe. If the Intensity of an AE changes, it's overall Intensity will be classified by the worst case of the multiple occurrences.

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.
- Missing severity will be assumed to be the worst severity case i.e. 'severe'; however, in the listing, it will be displayed as missing.

Seriousness will be assessed as either Not Serious or Serious, which is defined as:

- Resulting in death
- Life-threatening
- Requiring inpatient hospitalization or prolonging of existing hospitalization
- Resulting in persistent disability/incapacity
- Congenital anomaly/birth defect

The causal relationship between the study drug and the AE will be characterized as “Unrelated”, “Possibly Related”, or “Related”. Missing relationship will be assumed to be the worst severity case (Related) in data summary tables; however, in listings it will be displayed as missing. If a subject reports the same AE more than once within an SOC/PT, the AE with the worst -case Intensity and Relationship to the study treatment will be used in the corresponding summaries. An AE that occurred one or more times on treatment period will contribute only one observation to the numerator. The denominator comprises all safety subjects exposed to ANB019.

Only TEAEs will be summarized and presented by SOC and PT. Listings will include all AEs, with TEAEs flagged.

#### **19.1.1. TREATMENT EMERGENT ADVERSE EVENTS**

A TEAE is defined as:

- A new event that occurs during or after first dose of study treatment, or
- Any event present at Baseline that worsens in either intensity or frequency after the first dose of study treatment.

In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case i.e. Treatment Emergent.

The following summary tables will be provided by system order class (SOC) and preferred term (PT):

- Number of subjects with at least one TEAE
- Number of subjects with at least one serious TEAE
- Number of subjects with at least one TEAE by severity

- Number of subjects with at least one TEAE by relationship to study drug
- Number of subjects with at least one TEAE leading to permanent discontinuation of study drug
- Number of subjects with at least one TEAE leading to interruption of study drug
- Number of subjects with at least one TEAE leading to subject withdrawal from study
- Number of subjects with at least one TEAE leading to death

#### **19.1.2. TEAEs LEADING TO DISCONTINUATION OF TREATMENT**

TEAEs leading to permanent discontinuation of study treatment will be identified by the “Drug permanently discontinued” option in the “Action taken with the study drug” question. A listing of all TEAEs leading to discontinuation of treatment will be provided.

#### **19.1.3. TEAEs LEADING TO WITHDRAWAL OF SUBJECTS**

TEAEs leading to the withdrawal of subjects will be identified by the AE eCRF, using the question “Did the AE cause the subject to discontinue from the study?” A listing of all TEAEs leading to withdrawal of subjects from the study will be provided.

#### **19.1.4. INFUSION RELATED AEs/INJECTION SITE REACTIONS**

Infusion related AEs/injection site reactions will be identified by the AE eCRF, using the question “Is this an infusion related AE or injection site reaction?” A listing of infusion related AEs/injection site reaction will be provided.

#### **19.1.5. ADVERSE EVENTS OF SPECIAL INTEREST**

AESIs will be identified by the AE eCRF, using the question “Is this Adverse Event of Special Interest (AESI)?” AESIs will be listed and summarized.

#### **19.1.6. SERIOUS ADVERSE EVENTS**

Serious adverse events (SAEs) will be identified by the AE eCRF, using the “Seriousness Criteria” question.

SAEs will be listed and summarized.

#### **19.1.7. AES LEADING TO DEATH**

AEs leading to death will be identified by the AE eCRF, using the “Fatal” option in the “Final Outcome” question. A listing of AEs leading to death will be provided.

#### **19.1.8. DISEASE RELATED AES**

Disease-related AEs will be identified by the AE eCRF, using the question “Is this a disease related event?” Disease-related AEs will be listed and summarized.

### **19.2. LABORATORY EVALUATIONS**

Results from the central and local laboratories will be captured in this study for the assessments of hematology, clinical chemistry, urinalysis, serum pregnancy, follicle stimulating hormone (FSH), viral serology and TB screening. For the detailed list refer to the protocol, Appendix 3.

A central laboratory will be used to perform all laboratory tests, except for the urine pregnancy dipstick and when the investigator needs to make an immediate decision for any safety concerns based on laboratory results. In the latter scenario, the test will be performed in duplicate i.e. one sample will be tested at the central laboratory and another at the local laboratory for more immediate results. Only the central laboratory test results will be summarised and reported.

Results for all laboratory parameters at each scheduled assessment will be presented in Système International (SI) units as follows:

- Summary statistics and listings for quantitative test results including change from Baseline, reference ranges and abnormal and out-of-range values.
- Summary statistics and listings for qualitative test results including abnormal values.

### **19.2.1. LABORATORY SPECIFIC DERIVATIONS**

Quantitative laboratory results reported as “< X”, i.e., below the lower limit of quantitation (BLQ), or “> X”, i.e. above the upper limit of quantitation (ULQ), will be converted to X for quantitative summaries, but will be presented as recorded, i.e., as “< X” or “> X” in the listings.

### **19.2.2. LABORATORY REFERENCE RANGES**

Quantitative laboratory results will be compared with the relevant laboratory reference ranges in Système International (SI) units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

### **19.3. ECG EVALUATIONS**

Results from the central Electrocardiogram (ECG) Reading Centre will not be captured in the Electronic Data Capture (EDC) unless clinically significant. Parameters include: Pulse rate (bpm), PR interval (msec), QRS interval (msec), QT interval (msec) and QTcF interval (msec).

The overall assessment of ECG (Investigator’s judgment) will be presented:

- Normal
- Abnormal, not clinically significant (ANCS)
- Abnormal, clinically significant (ACS)

ECG test results will be presented as a summary of shift from Baseline in overall assessment, and a listing of clinically significant abnormalities.

### **19.4. VITAL SIGNS**

Vital signs data at each scheduled assessment will be presented as follows as summary statistics including change from Baseline: axillary body temperature (<sup>0</sup>C/F), measured once; supine pulse rate (bpm), measured once; respiratory rate (resp/min), measured once; and supine blood pressure, measured twice. The average



of the two readings will be entered in eCRF. The listing will include an indicator of markedly abnormal results.

Body temperature will be presented in °C. All values in °F will be converted as follows:

$$^{\circ}\text{C} = (^{\circ}\text{F} - 32) / 1.8$$

## 19.5. PHYSICAL EXAMINATION

The following assessments will be taken at every physical examination: general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, and musculoskeletal system; extremities; eyes; nose; throat; and neurologic status.

Results will be captured by the following categories:

- Normal
- Abnormal, not clinically significant (ANCS)
- Abnormal, clinically significant (ACS)

Only abnormal findings will be presented in listings.

## 19.6. OTHER SAFETY ASSESSMENTS

### 19.6.1. BIOMARKER ANALYSIS

Skin biopsies will be performed to measure biomarkers. All subjects enrolled in the study will be asked to participate in the skin biopsy analysis; however, participation is optional, and subjects will be asked to give specific consent for these assessments.

Measurements may include immunohistochemistry and RT-PCR to assess psoriasis associated markers of inflammation (IL-17, IL-23, IL-8, dendritic cells, epidermal thickness, and leukocytes infiltration). Observed and change from baseline in serum cytokine concentrations to days 3, 8, 29, 57, 85, 113 and 169 will be analyzed using paired t-tests when adequate data exists. Change from Baseline for the SAF will be presented with the mean (SD) and nominal p-value.

The relationship between ANB019 concentrations and biomarker endpoints will be explored graphically.

### **19.6.2. IMMUNOGENICITY ANALYSIS**

Antibodies to ANB019 will be evaluated in serum samples collected from all subjects. These samples will be tested by AnaptysBio or Sponsor designee.

Observed values for ADA status/titers will be listed and summarized for the SAF.

If data permits, any correlation between ADA status and safety and efficacy endpoints will be evaluated.

## **20. GENETIC ANALYSIS**

### **20.1. GPP ASSOCIATED MUTATIONS**

Whole blood collection samples for DNA and mRNA will be obtained for genetic analysis to evaluate the impact of genetic variation on a subject's response to the study treatment, for their susceptibility to the disease, and for their severity and progression of the disease.

All subjects enrolled in the study will be asked to participate in the genetic analysis; however, participation is optional, and subjects will be asked to give specific consent for these assessments.

Samples will be sent to the designated laboratory for genetic and bioinformatic analysis. Results may be reported in the clinical study report (CSR) or in a separate study summary.

## **21. DATA NOT SUMMARIZED OR PRESENTED**

The other variables and/or domains not summarized or presented are:

Photographic documentation of lesions

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.



## 22. REFERENCES

Protocol: ANB019\_002\_Protocol\_Amendment 4\_final\_\_16Aug 2019.docx.pdf

eCRF: ANB019-002\_ASB\_V05\_06MAR2019.pdf

<http://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=1653>

[https://www.medcalc.org/manual/logistic\\_regression.php](https://www.medcalc.org/manual/logistic_regression.php)



## APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

### OUTPUT CONVENTIONS

#### Output File Naming Conventions

- o File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.
- o As far as possible, output files should be in RTF format, although .DOC files are also permitted.
- o The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure).
- o If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g. T14\_3\_01.RTF).

#### Paper Size, Orientation and Margins

- o The size of paper will be Letter for the United States (Letter), otherwise A4.
- o The page orientation should preferably be landscape, but portrait is also permitted.
- o Margins should provide at least 1 inch (2.5 centimeters) of white space all around the page, regardless of the paper size.
- o The number of columns per page (linesize) should be 145 for A4 and 134 for Letter.
- o The number of rows per page (pagesize) should be 49 for A4 and 51 for Letter.

#### Fonts

- o The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8.
- o The font color should be black. No bolding, underlining, italics or subscripting are permitted. Avoid using super-scripts, unless absolutely necessary.
- o Single spacing should be used for all text.

- o Figures should have a default font of “Times Roman”, “Helvetica”, or “Courier New”. This can be achieved by using the following options in SAS:

goptions

gunit = pct

cback = white

colors = (black)

hby = 2.4

ftext = "TimesRoman"

htext = 2.5

device = cgmof97l

gaccess = gsasfile;

filename gsasfile "...cgm";

Headers

- o The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing.
- o The customer name and protocol number should appear in row 1, left-aligned.
- o The output identification number should appear in row 2, centered.
- o The output title should start in row 3, centered.
- o The output population should appear in row 4, centered. The population should be spelled out in full, e.g. Intention-to-Treat in preference to ITT.
- o Row 5 should be a continuous row of underscores (‘\_’). The number of underscores should equal the linesize).
- o Row 6 should be a blank line.
- o Mixed case should be used for titles.
- o The output titles should be designed so that they are arranged consistently through all outputs, e.g. content (e.g. Vital Signs) followed by metric (e.g. Change from Baseline) e.g. Vital Signs – Change from Baseline.
- o Titles should not contain quotation marks or footnote references.
- o The column headings should be underlined with a row of underscores (‘\_’).
- o Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.

- o Column headings containing numbers should be centered.
- o Column headings should be in sentence case.
- o In general, the population count should appear in the column header in the form “(N=XXX)”.
- o “Statistic” should be the column header over n, Mean, SE, n (%) etc.
- o As a rule, all columns should have column headings.

#### Table and Listing Output Conventions

##### General:

- o The first row in the body of the table or listing should be blank
- o The left -hand column should start in column 1. No indenting or centering of the output should occur.
- o Rounding should be done with the SAS function ROUND.
- o Numbers in tables should be rounded, not truncated.
- o Alphanumeric output should be left aligned.
- o Numbers should be decimal point aligned.
- o Whole numbers should be right aligned.
- o Text values should be left aligned.
- o The first letter of a text entry should be capitalized i.e. use sentence case, unless otherwise indicated.
- o Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- o If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- o All listing outputs should be sorted (preferably by Site Number and Subject Number).
- o Do not use superscripts and subscripts.
- o Exponentiation will be expressed using a double asterisk, e.g. mm<sup>3</sup> will be written as mm\*\*3.
- o All variables that are output in the eCRF (which have data present) should appear in the listings, along with all derived data appearing in the corresponding tables.
- o The width of the entire output should match the linesize.

##### Univariate Statistics:

- o Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)

- o Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- o If the original data has N decimal places, then the summary statistics should have the following decimal places:

Minimum and maximum: N

Mean, median and CV%: N + 1

Standard deviation/error (SD/SE): N + 2

#### Frequencies and percentages (n and %):

- o Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

77 (100.0%)

50 ( 64.9%)

0 ( 0.0%)

- o Percentages will be reported to one decimal place, except in the following cases:

Percentages <100.0% but >99.9%, e.g. 99.99% will be presented as '>99.9%'.

Percentages < 0.1%, e.g. 0.08% will be presented as '<0.1%'.

- o Rounding will be applied after the <0.1% and >99.9% rule.
- o Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- o Where counts are zero, percentages of 0.0% should appear in the output.

#### Confidence Intervals:

- o As a rule, confidence intervals are output to one decimal place more than the raw data.
- o Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- o Boundary values of confidence intervals should be separated by a comma.

- o Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place. An example is given below:

(-0.12, -0.10)

9.54, 12.91)

P-values:

- o P-values should be reported to three decimal places, except in the following cases:

Values  $<1.000$  but  $>0.999$ , e.g. 0.9998, will be presented as ' $>0.999$ '.

Values  $<0.001$ , e.g. 0.0009, will be presented as ' $<0.001$ '.

- o Rounding will be applied after the  $<0.001$  and  $>0.999$  rule.

Ratios:

- o Ratios should be reported to one more decimal place than the original data.

Spacing:

- o There must be a minimum of 1 blank space between columns (preferably 2).

Denominators:

- o If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- o Alternatively, a footnote should be included in each table with percentages, to indicate the denominator for percentages.

Missing values

- o A "0" should be used to indicate a zero frequency. Do not show a percentage.
- o For descriptive statistics where  $n=0$ , a blank should be used for the rest of the statistics (standard deviation, mean, etc.).
- o For descriptive statistics where  $n=1$ , a "N/a" should be used for the standard deviation.
- o A blank will be used to indicate missing data in an end-of-text table or subject listing.

Figure Output Conventions



- o Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
- o The CGM file itself should contain the title or footer.
- o The image should be clear and of high quality when viewed in the Word document, and when printed.
- o In general, boxes should be used around the figures.

#### Footnote Information

Footers should be defined as follows:

- o A continuous line of underscores ('\_') will follow the body of the table or listing prior to any footnotes at the bottom of the page.
- o Table footnotes should be defined using *compute* statements in the *proc report*, and should appear directly after the body of the table.
- o The program path, name and version number (if applicable) should appear as footnote 1 at the bottom of the page.
- o The date/time stamp should appear as footnote 2 at the bottom of the page
- o Footnotes should be left-aligned.
- o Footnotes should be in sentence case.
- o Only “typewriter” symbols are permitted, e.g. “\*”, “\$”, “#”, “@”, “&” and “+”.
- o The choice of footnote symbols should be consistent, e.g. if you have the footnote “# indicates last observation carried forward” for one table, the same symbol and footnote should indicate LOCF for all tables.
- o If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
- o The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in the first footnote, right aligned.

Ordering of footnotes should be as follows:

- 1.) Source data listing reference, if necessary
- 2.) Abbreviations and definitions
- 3.) Formulae
- 4.) P-value significance footnote

- 5.) Symbols
- 6.) Specific notes
  - o Common notes from table to table should appear in the same order.
  - o The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

## **DATES & TIMES**

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

## **SPELLING FORMAT**

The spelling format to be used is US English.

## **PRESENTATION OF TREATMENT GROUPS**

For outputs, treatment groups will be represented as “Total” in tables, listings and graphs.

## **PRESENTATION OF VISITS**

For outputs, visits will be represented as follows and in that order:

<b>Long Name</b>	<b>Short Name</b>
Screening	Screening
Day 1 Visit 1	Day 1
Day 3 Visit 2	Day 3
Day 8 Visit 3	Day 8
Day 15 Visit 4	Day 15

<b>Long Name</b>	<b>Short Name</b>
Day 22 Visit 5	Day 22
Day 29 Visit 6	Week 4
Day 43 Visit 7	Day 43
Day 57 Visit 8	Day 57
Day 71 Visit 9	Day 71
Day 85 Visit 10	Day 85
Day 113 Visit 11	Week 16
Day 141 Visit 12	Day 141
Day 169 Visit 13	Day 169
End of Study	EOS
Unscheduled	Unscheduled

## **LISTINGS**

All listings will be ordered by the following (unless otherwise indicated in the template):  
Study center-subject ID then Date (and time, where applicable), with Study Day in brackets.



## APPENDIX 2. PARTIAL DATE CONVENTIONS

### ALGORITHM FOR TREATMENT EMERGENT ADVERSE EVENTS

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE

START DATE	STOP DATE	ACTION
		If stop date $\geq$ study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date $<$ study med start date, then not TEAE If stop date $\geq$ study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date $<$ study med start date, then not TEAE If stop date $\geq$ study med start date, then TEAE
	Missing	Assumed TEAE

**ALGORITHM FOR PRIOR/CONCOMITANT MEDICATIONS**

START DATE	STOP DATE	ACTION
Known	Known	If (stop date $<$ study treatment start date), assign as prior If (stop date $\geq$ study treatment start date) and (start date $\leq$ end of treatment), assign as concomitant If (stop date $\geq$ study treatment start date) and (start date $>$ end of treatment), assign as post treatment



START DATE	STOP DATE	ACTION
	Partial	<p>Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:</p> <p>If (stop date &lt; study med start date), assign as prior</p> <p>If (stop date &gt;= study med start date) and (start date &lt;= end of treatment), assign as concomitant</p> <p>If (stop date &gt;= study med start date) and (start date &gt; end of treatment), assign as post treatment</p>
	Missing	<p>If stop date is missing, medication can never be assumed as prior</p> <p>If (start date &lt;= end of treatment), assign as concomitant</p> <p>If (start date &gt; end of treatment), assign as post treatment</p>
Partial	Known	<p>Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:</p> <p>If (stop date &lt; study med start date), assign as prior</p> <p>If (stop date &gt;= study med start date) and (start date &lt;= end of treatment), assign as concomitant</p> <p>If (stop date &gt;= study med start date) and (start date &gt; end of treatment), assign as post treatment</p>
	Partial	<p>Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:</p> <p>If (stop date &lt; study med start date), assign as prior</p> <p>If (stop date &gt;= study med start date) and (start date &lt;= end of treatment), assign as concomitant</p> <p>If (stop date &gt;= study med start date) and (start date &gt; end of treatment), assign as post treatment</p>

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing, medication can never be assumed as prior If (start date <= end of treatment), assign as concomitant If (start date > end of treatment), assign as post treatment
Missing	Known	If (stop date < study med start date), assign as prior If (stop date >= study med start date), assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If (stop date < study med start date), assign as prior If (stop date >= study med start date), assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant



